REMARKS

Claims 28-52 are pending in this application. Claims 1-27 have been canceled without prejudice or disclaimer.

Independent claim 28 is directed to a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and colloidal particles, said particles comprising approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer, wherein said protein or polypeptide is selected from the group consisting of: (a) proteins or polypeptides capable of externally binding said colloidal particles; (b) proteins or polypeptides capable of binding polymers of the polyalkylether, polylactic and polyglycolic acid families; and (c) proteins or polypeptides that include a consensus sequence of S/T-X-L/I/V-I/V/Q/S-S/T-X-X-E, where X may be any amino acid, and S, T, L, I, V, E and Q have their standard meanings; wherein said protein or polypeptide is not Factor VIII (FVIII), and wherein said protein or polypeptide is not encapsulated in said colloidal particles. Claims 29-46 depend, either directly or indirectly, from claim 28.

Independent claim 47 is directed to a method of treatment of a patient suffering from a disease comprising administrating to said patient a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide effective in the treatment of the disease and colloidal particles, said colloidal particles comprising approximately 1-20 mole percent of an amphipathic lipid derivatized with a

biocompatible hydrophilic polymer, wherein said protein or polypeptide is selected from the group consisting of: (a) proteins or polypeptides capable of externally binding said colloidal particles; (b) proteins or polypeptides capable of binding polymers of the polyalkylether, polylactic and polyglycolic acid families; and (c) proteins or polypeptides that include a consensus sequence of S/T-X-L/I/V-I/V/Q/S-S/T-X-X-E, where X may be any amino acid, and S, T, L, I, V, E and Q have their standard meanings; wherein said protein or polypeptide is not Factor VIII (FVIII), and wherein said protein or polypeptide is not encapsulated in said colloidal particles. Claims 48-52 depend, either directly or indirectly, from claim 47.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

I. At page 2 of the Official Action, the title is objected to.

The Examiner asserts that the title is objected to as being to long. More specifically, the Examiner asserts that "the title is limited to 2-7 words maximum." Accordingly, the Examiner requests a new title.

In view of the remarks set forth herein, Applicants respectfully traverse this rejection.

37 CFR § 1.72 (a) provides that:

> The title of the invention may not exceed 500 characters in length and must be as short and specific as possible. Characters that cannot be captured and recorded in the Office's automated information systems may not be reflected in the Office's records in such systems or in documents created by the Office. Unless the title is supplied in an application data sheet (§ 1.76), the title of the

invention should appear as a heading on the first page of the specification. *See* 37 CFR § 1.72 (a) as well as MPEP § 606.

Applicants respectfully submit that the present title fully complies with 37 CFR § 1.72 because the present title is brief, technically accurate and descriptive of the pending claims. Specifically, the presently pending claims are generally directed to pharmaceutical compositions for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and colloidal particles and methods of treating a patient suffering from a disease comprising administrating to said patient a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide effective in the treatment of the disease and colloidal particles. *See* generally, claims 28 and 47. Accordingly, each of the presently pending claims is encompassed by the present title, "PHARMACEUTICAL COMPOSITION COMPRISING PROTEINS AND/OR POLYPEPTIDES AND COLLOIDAL PARTICLES."

Additionally, the presently pending title is far shorter than 500 characters in length. In fact, including spaces, the present title is merely 90 characters in length. Accordingly, the length of the present title is well within the length allowable under 37 CFR § 1.72(a).

Therefore, it is submitted that the present title meets the requirements of 37 CFR § 1.72(a). Accordingly, the Examiner is respectfully requested to withdraw this objection.

II. At page 2 of the Official Action, claims 28, 47, 50 and 51 have been rejected under 35 USC § 112, first paragraph.

The Examiner asserts that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims. Specifically, the Examiner asserts that while the specification is "enabling for hemophilia, [it] does not reasonably provide enablement for any other diseases, disorders or conditions." *See* the sentence bridging pages 2 and 3.

In view of the following, this rejection is respectfully traversed.

From the outset Applicants note that it appears that the Examiner has misapplied the rejection to claim 28. Specifically, ***claim 28 is a composition claim that does not indicate any disease, disorder or condition***, either generally or otherwise. In this regard, the intended use of claim 28 does not bear any weight on the enablement of the claim. As provided in MPEP § 2164.01(c):

> When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (claiming a chimeric gene capable of being expressed in any cyanobacterium and thus defining the claimed gene by its use).
>
> In contrast, ***when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use***. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. ***In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention***. *See* MPEP § 2164.01(c). (Emphasis Added).

With regard to the rejection of claims 47, 50 and 51, Applicants politely remind the Examiner that responsive to the election of species required by the Examiner in the Official Action of May 10, 2007, Applicants have elected the species G-CSF as the "specific protein or polypeptide," and multiple sclerosis as the disease for examination on the merits. Accordingly, Applicants note that pursuant to the Examiner's required election of species, the Examination of the present claims is limited to the elected species. However, Applicants respectfully submit that in addition to claims 47, 50 and 51 being fully enabled for a method of treating a patient suffering from multiple sclerosis with G-CSF, the claims are fully enabled for other diseases which may be treated by the proteins and polypeptides disclosed in the specification.

Further, Applicants note that presently claimed subject matter is not concerned with a new indication of treatment for a known protein, but rather with enhancing the therapeutic effect of known proteins for known diseases by increasing their half-life in the bloodstream. *See* the present specification at page 3, lines 4-5. Thus, one of ordinary skill in the art would know which diseases may be treated by the proteins used in the invention, which patient populations are involved, and what dosages are to be used.

The enablement provision of the Patent Act requires that the patentee provide a written description of the invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." 35 U.S.C. § 112, first paragraph (2000). The purpose of this requirement is to ensure that "the

public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims." *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195-96 (Fed. Cir. 1999); *see also* Donald S. Chisum, 3 *Chisum on Patents* § 7.01 (2002).

Accordingly, the specification must provide sufficient teaching such that one skilled in the art could make and use the full scope of the invention without undue experimentation. *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003); *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997); *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). "The key word is 'undue,' not experimentation.'" *Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Routine experimentation does not constitute undue experimentation. *See Johns Hopkins University v. Cellpro, Inc.,* 152 F.3d 1342 (Fed. Cir. 1998). That is, the specification need only teach those aspects of the invention that one skilled in the art could not figure out without undue experimentation. *See, e.g., Nat'l Recovery Techs.*, 166 F.3d at 1196 ("The scope of enablement . . . is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation."); *Wands*, 858 F.2d at 736-37 ("Enablement is not precluded by the necessity for some experimentation such as routine screening."). "Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *See In re Wright,* 999 F.2d 1557 (Fed. Cir. 1993).

Although the ultimate determination of whether one skilled in the art could make and use the claimed invention without undue experimentation is a legal one, it is based on underlying findings of fact. *CFMT*, 349 F.3d at 1337. Furthermore, "[w]hether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *Wands*, 858 F.2d at 737.

Some of these considerations, commonly referred to as "the *Wands* factors," include "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *Id.; see also Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991) (stating that the *Wands* factors "are illustrative, not mandatory" and that what is relevant to an enablement determination depends upon the facts of the particular case).

With regard to the presently pending claims, Applicants respectfully submit that the specification, figures, and experimental examples, provide ample guidance to the skilled artisan in view of the state of the art at the time the application was filed, to make and use the claimed invention without undue experimentation.

Additionally, Applicant respectfully submit that that the court in *In re Wright* held that nothing more than objective enablement is required, and therefore it is

irrelevant whether this teaching is provided through broad terminology or illustrative examples.

In the present case, Applicants assert that the specification, figures, and examples, provide ample guidance to the skilled artisan in view of the state of the art at the time the application was filed, to make and use the claimed subject matter without undue experimentation.

Applicants note that the Examiner's citation of Tomkins et al., "An array of possibilities for multiple sclerosis," *Nature Medicine*, May 2002, 8(5): 451-453, shows a nexus between the treatment of Multiple Sclerosis and the administration of a composition comprising G-CSF. Therefore, Applicants submit that the Examiner shows, on the record, that G-CSF is useful in the treatment of Multiple Sclerosis. Tomkins et al. utilize a mouse model of Multiple Sclerosis, experimental autoimmune encephalomyelitis (EAE), to provide a model that "will directly affect studies with MS patients by providing data to help explain clinical trials, as well as initiate new investigations." *See* Tomkins et al. at page 453. For example, as described in the paragraph bridging columns 2 and 3 on page 452 of Tomkins et al., "...Treatment with G-CSF before the onset of disease decreased the severity of the early stages of the disease." *See* Tompkins et al. at page 453. Additionally, "G-CSF may be expressed early as a mechanism to down regulate acute disease." *Id.*

In further support of Applicants position, Applicants provide herewith a copy of each of a Declaration under 37 CFR § 1.132, executed by Dr. Moshe Baru; Annex A; and Annex B. As indicated in paragraph 1 of the Declaration,

Annex A is a copy of Dr. Baru's Curriculum Vitae. As indicated in paragraph 3 of the Declaration, Annex B describes the results of an experiment preformed by Dr. Baru in which a composition comprising G-CSF (prepared according to the present specification) is utilized for the treatment of neutropenia and for mobilization of stem cells into peripheral blood.

According to Dr. Baru, while the present specification describes experimental results related to hemophilia, these results are representative of other diseases which may be treated with the compositions of the present claims. *See* the Declaration at paragraph 3. In this regard, Dr. Baru indicates that the results of the experiments described in Annex B may be used to provide a reasonable basis for the assumption that a composition comprising G-CSF may be used to treat other diseases for which G-CSF is known to be effective.

Regarding neutropenia, two experiments were preformed by Dr. Baru. In one experiment, male Spargue-Dawley (SD) rats (6-8 weeks old, ~200g) received a single intraperitoneal (i.p) dose of 100mg/kg cyclophosphamide (CP) at day 0 to induce neutropenia. On days 1, 2, and 3 rats received a single daily subcutaneous (s.c) injection of vehicle (5% glucose), 30µg/kg of free G-CSF, or 30µg/kg of PEGylated liposome-formulated G-CSF (PEGLip-G-CSF). All rats were weighed daily. Rats treated with G-CSF were bled prior to CP injection, prior to the first G-CSF injection, and at 8, 24, 32, 48, 56, and 72 hours following the first G-CSF injection. Control rats were bled prior to CP injection, prior to the first injection of vehicle, and at 24, 48, and 72 hours following the first injection of vehicle. White blood cell counts and differential counts of neutrophils,

eosinophils, basophils, monocytes and lymphocytes were determined for each blood sample. *See* page 1 of Annex B.

In a second experiment, guinea pigs (6-8 weeks old, ~400g) received a single i.p dose of 100mg/kg CP at day 0 to induce neutropenia. On days 5, 6, and 7 guinea pigs received a single daily (s.c) injection of vehicle (5% glucose), 30 µg /kg of free G-CSF, or 30µg/kg of PEGLip-G-CSF. All guinea pigs were weighed daily. Guinea pigs treated with G-CSF were bled prior to CP injection, prior to the first G-CSF injection, and at 8, 24, 32, 48, 56, 72, and 96 hours following the first G-CSF injection. Control guinea pigs were bled prior to CP injection, prior to first injection of vehicle, and at 24, 48, 72 and 96 hours following the first injection of vehicle. White blood cell counts and differential counts of neutrophils, eosinophils, basophils, monocytes and lymphocytes were determined for each blood sample. *See* Annex B at page 5.

The results of the experiments indicate that PEGLip-G-CSF is more effective than free G-CSF in enhancing white blood cells and neutrophils counts in both neutropenic rats and guinea pigs and the injection of PEGLip-G-CSF resulted in an increase of ~50% in white blood count AUC and absolute neutrophil count AUC versus that of free G-CSF. *See* Annex B at page 5.

Additionally, as described in Annex B, Dr. Baru evaluated the mobilization of stem cells into peripheral blood by G-CSF and PEGLip-G-CSF. In the experiment, Neupogen (96µg/ml) was mixed with 5% glucose or 9% PEGLip solutions to a final G-CSF concentration of 75µg/ml (final liposome concentration in the mix was ~8.3%). Mixtures were incubated for 20 min at room temp, rolling.

Balb/C male mice were injected IV with 5% glucose solution or with 300µg/kg of each of G-CSF formulations (Free or PEGLip). Mice were injected daily for 5 days, and were bled 3h after the last injection (99h) from the retro-orbital sinus into EDTA tubes. *See* Annex B at page 5.

Mice blood of each group was pooled, and blood cells were washed with PBS/ 0.5% BSA. Washed packed cells were FcR blocked with mouse IgG to reduce non-specific antibody binding, and then incubated with FITC labeled antibodies against lineage markers (CD3, CD45R, CD11b, Gr-1) and PE labeled anti stem cell antigen 1 (sca-1) antibody. Cells were analyzed by flow cytometry and the number of stem cells (Lineage negative and sca-1 positive cells) in peripheral blood was determined. According to the results of the experiment, it was determined that PEGLip-G-CSF is more effective than free G-CSF in enhancing mobilization of stem cells into the peripheral blood. *Id.*

In view of Tomkins et al. as well as the Declaration and supporting documents submitted herewith, Applicants respectfully submit that the specification, figures, and experimental examples, provide ample guidance to the skilled artisan in view of the state of the art at the time the application was filed, to make and use the claimed invention without undue experimentation.

Therefore, Applicants submit that the present specification enables the skilled artisan to make and use the full scope of claims 28, 47, 50 and 51 within the meaning of 35 USC § 112, first paragraph. Thus, the Examiner is respectfully requested to withdraw this rejection.

III. At page 11 of the Official Action, claims 28-43 and 46 are rejected under 35 USC § 103(a) as being unpatentable over Martin et al. in view of Collins et al. and Zalipsky.

The Examiner asserts that it would have been obvious to combine the teachings of Martin et al. (US Patent No. 5,225,212) in view of Collins et al. (US Patent No. 5,874,075) and Zalipsky (US Patent No. 6,586,001) to obtain the subject matter of claims 28-43 and 46.

Applicant respectfully traverses this rejection because a *prima facie* case of obviousness has not been established.

A brief outline of relevant authority, is set forth below.

To establish a *prima facie* case of obviousness, the Examiner must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost

of necessity will be combinations of what, in some sense, is already known." (*KSR*, *supra*, slip opinion at 13-15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Regarding motivation to combine references, **MPEP 2143** discusses the requirements of a *prima facie* case of obviousness. First, there must be some suggestion or motivation to combine the reference teachings or to modify the reference, and second, there must be a reasonable expectation of success. Finally, the prior art reference or references when properly combined, must teach or suggest all the claim limitations.

MPEP 2143.01 states that there are three possible sources for "a motivation" to combine references: the nature of the problem being solved; the teachings of the prior art; and the knowledge of one of ordinary skill in the art. Further, **MPEP 2145(X)(D)(2)** states that "It is improper to combine references where the references *teach away* from there combination."

Regarding motivation to modify properly combined references, **MPEP 2143** states that where the prior art conflicts, all teachings must be considered and that the fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness. **MPEP 2143** further states that there must be some suggestion or motivation to modify the references, and there must be a

reasonable expectation of success. In addition, the prior art reference or references when properly combined, must teach or suggest all the claim limitations.

MPEP 2143.01 states that a proposed modification cannot render the prior art unsatisfactory for its intended purpose. If it does, then there is no suggestion or motivation to make the proposed modification. Further, the proposed modification cannot change the principle operation of a reference.

It is submitted that a proper case of *prima facie* obviousness has not been established because, whether taken alone or in combination, none of Martin et al., Colins et al. or Zalipsky teach or suggest a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and colloidal particles, wherein the protein or polypeptide is not encapsulated in the colloidal particles, as required by the present claims.

Claim 28 is directed to a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and colloidal particles, said particles comprising approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer, wherein said protein or polypeptide is selected from the group consisting of: (a) proteins or polypeptides capable of externally binding said colloidal particles; (b) proteins or polypeptides capable of binding polymers of the polyalkylether, polylactic and polyglycolic acid families; and (c) proteins or polypeptides that include a consensus sequence of S/T-X-L/I/V-I/V/Q/S-S/T-X-X-E, where X may be any amino acid, and S, T, L, I, V, E and Q have their

standard meanings; wherein said protein or polypeptide is not Factor VIII (FVIII), and ***wherein said protein or polypeptide is not encapsulated in said colloidal particles***. (Emphasis added). Claims 29-29-43 and 46 depend, either directly or indirectly, from claim 28.

In contrast, Martin et al. is directed to a liposome composition for extended release of a therapeutic compound into the bloodstream. According to Martin et al. liposomes are composed of vesicle-forming lipids and between 1-20 mole percent of a vesicle-forming lipid derivatized with hydrophilic polymer, have sizes in a selected size range between 0.1 and 0.4 microns, and contain the therapeutic compound in liposome-entrapped form. *See* Martin et al. , abstract. According to Martin et al., ***the therapeutic compound is encapsulated within the liposome***. *See* Martin et al. at columns 11 and 12.

In contradistinction, according to the present subject matter, the protein or polypeptide is not encapsulated in the colloidal particles. As disclosed in the present specification, a liposome is first formed, and afterwards mixed with an active compound, so that the compound is not encapsulated in the liposome. *See* the present specification at page 13, lines 14-18. Therefore, Applicants submit that Martin et al. fail to teach or suggest a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and colloidal particles, wherein the protein or polypeptide is not encapsulated in the colloidal particles, as required by the present claims.

Collins et al. fail to remedy the deficiencies of Martin et al. Collins et al. is directed to stable compositions of proteins and related methods, wherein a

protein capable of transitioning into the molten globular state is contacted with a negatively charged lipid vesicle, thereby stabilizing the protein against thermally-induced aggregation, denaturation, and loss of activity. The protein/phospholipid complex of Collins et al. directly stabilizes the secondary and tertiary structure of the protein, and the compositions are useful in high temperature formulations and in novel delivery vehicles. *See* Collins et al. , abstract.

Collins et al. differs from the presently claimed subject matter in several ways. First, Collins et al. relates only to proteins capable of transitioning into the molten globular state. *See* Collins et al. at column 7, lines 41-54. In contrast, the presently claimed subject matter relates to other types of proteins. Further, Collins et al. is directed to only negatively-charged liposomes. *See* Collins et al. at column 4, lines 30-45. In contrast, the presently claimed subject matter is directed to neutral liposomes. *See* presently pending claim 29. Additionally, in Collins et al., the hydrophilic polymer (=PEG) is bound to the protein to produce PEGylated G-CSF. *See* Collins et al. at column 8, lines 26-32. According to the present subject matter the hydrophilic polymer is bound to the lipid, and not to the protein, which is not PEGylated. Most importantly, the proteins used in the composition of Collins et al. are embedded in the liposome membrane. *See* Collins et al. at Example I, column 15, lines 14-64. Therefore, Applicants submit that, like Martin et al., Collins et al. fail to teach or suggest a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and colloidal particles, wherein the protein or polypeptide is not encapsulated in the colloidal particles, as required by the

present claims. Accordingly, whether taken alone or in combination neither of Martin et al. and Collins et al. teach or suggest every element of the presently claimed subject matter.

Zalipsky does not remedy the deficiencies of Martin et al. and Collins et al. Zalipsky is directed to liposomes containing PEG-substituted neutral lipopolymers. In general, Zalipsky does not expressly teach or suggest the location of the protein. However, Zalipsky does disclose that by using an uncharged lipid, there is reduced leakage of an encapsulated cationic drug. *See* Collins et al. at column 4, lines 22-24. Therefore, Applicants submit that, like Martin et al. and Collins et al., Zalipsky also fails to teach or suggest a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and colloidal particles, wherein the protein or polypeptide is not encapsulated in the colloidal particles, as required by the present claims. Accordingly, whether taken alone or in combination neither of Martin et al., Collins et al. and Zalipsky teach or suggest every element of the presently claimed subject matter.

In view of the remarks set forth herein, it is submitted that, whether taken alone or in combination, Martin et al., Collins et al. and Zalipsky do not render claims 28-43 and 46 obvious within the meaning of 35 USC § 103 (a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

IV. At page 14 of the Official Action, claims 47, 50 and 51 are rejected under 35 USC § 103(a) as being unpatentable over Martin et al. in view of Collins et al. and Zalipsky as applied to claims 28-43 and 46 above, and in further view of Habberfield (PG Pub. 2002/0099001) and Tomkins et al.

The Examiner asserts that it would have been obvious to combine the teachings of Martin et al. in view of Collins et al. and Zalipsky (US Patent No. 6,586,001) to obtain the subject matter of claims 28-43 and 46.

Applicant respectfully traverses this rejection because *prima facie* case of obviousness has not been established.

A brief outline of relevant authority, is set forth above.

It is submitted that a proper case of *prima facie* obviousness has not been established because, whether taken alone or in combination, none of Martin et al., Colins et al., Zalipsky, Habberfield et al., and Tompkins et al. teach or suggest a method of treatment of a patient comprising administering to said patient pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and colloidal particles, wherein the protein or polypeptide is not encapsulated in the colloidal particles, as required by the present claims.

Claim 47 is directed to a method of treatment of a patient suffering from a disease comprising administrating to said patient a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide effective in the treatment of the disease and colloidal particles, said colloidal particles comprising approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer,

wherein said protein or polypeptide is selected from the group consisting of: (a) proteins or polypeptides capable of externally binding said colloidal particles; (b) proteins or polypeptides capable of binding polymers of the polyalkylether, polylactic and polyglycolic acid families; and (c) proteins or polypeptides that include a consensus sequence of S/T-X-L/I/V-I/V/Q/S-S/T-X-X-E, where X may be any amino acid, and S, T, L, I, V, E and Q have their standard meanings; wherein said protein or polypeptide is not Factor VIII (FVIII), and ***wherein said protein or polypeptide is not encapsulated in said colloidal particles***. (Emphasis added). Claims 50 and 51 depend, either directly or indirectly, from claim 47.

Each of Martin et al., Colins et al. and Zalipsky is discussed above. As indicated Applicants submit that none of Martin et al., Colins et al. and Zalipsky teach or suggest a method of treatment of a patient comprising administering to said patient pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and colloidal particles, wherein the protein or polypeptide is not encapsulated in the colloidal particles, as required by the present claims.

Habberfield does not remedy the deficiencies of Martin et al., Colins et al. and Zalipsky. Habberfield is directed to compositions and methods for oral delivery of chemically modified proteins, including chemically modified G-CSF and chemically modified consensus interferon. *See* Habberfield , abstract. Like the other applied references, Habberfield does not teach or suggest a method of treatment of a patient comprising administering to said patient pharmaceutical

composition for ***parenteral*** administration comprising a therapeutically effective amount of a protein or polypeptide and colloidal particles, ***wherein the protein or polypeptide is not encapsulated in the colloidal particles***, as required by the present claims. Therefore, Applicants submit that whether taken alone or in combination, none of Martin et al., Colins et al., Zalipsky and Habberfield teach or suggest all of the elements of the presently pending claims.

Tompkins et al. do not remedy the deficiencies of Martin et al., Colins et al., Zalipsky and Habberfield. Tompkins et al. is directed to a mouse model of Multiple Sclerosis, experimental autoimmune encephalomyelitis (EAE), to provide a model that "will directly affect studies with MS patients by providing data to help explain clinical trials, as well as initiate new investigations." *See* Tomkins et al. at page 453. However, in contrast to the presently pending claims, Tompkins et al. fails to teach or suggest a method of treatment of a patient comprising administering to said patient pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and colloidal particles, ***wherein the protein or polypeptide is not encapsulated in the colloidal particles***. Therefore, Applicants submit that whether taken alone or in combination, none of Martin et al., Collins et al., Zalipsky, Habberfield and Tomkins et al. teach or suggest all of the elements of the presently pending claims.

In view of the remarks set forth herein, it is submitted that, whether taken alone or in combination, Martin et al., Collins et al., Zalipsky, Habberfield and Tomkins et al. do not render claims 47 and 50-51 obvious within the meaning of

35 USC § 103 (a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

V. At page 17 of the Official Action, claims 28-33 and 39-43 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of US Patent No. 6,930,087 in view of Collins et al.

The Examiner asserts that if one of ordinary skill in the art practiced the invention of US Patent No. 6,930,087 in view of Collins et al., one would necessarily achieve the presently claimed subject matter.

Applicants respectfully traverse this rejection.

Applicants note that the present application and US Patent No. 6,930,087 are commonly owned. Accordingly, Applicants submit herewith a Terminal Disclaimer in compliance with 37 CFR § 1.321 disclaiming any statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the statutory term defined in 35 USC §§ 154-156 and 173 of US Patent No. 6,930,087.

In view of the submission of the referenced terminal disclaimer, the Examiner is respectfully requested to withdraw this rejection.

VI. Claims 28-33 and 39-43 have been rejected under 35 USC § 103(a) as being obvious over Baru et al. (US Patent No. 6,930,087) in view of Collins et al.

The Examiner asserts that it would have been obvious to combine the teachings of Baru et al. with the teachings of Collins et al. to obtain the subject matter of claims 28-33 and 39-43.

Applicant respectfully traverses this rejection because a *prima facie* case of obviousness has not been established.

Recently, the Federal Circuit in *Takeda Chemical Industries v. Alphapharm*, No. 06-1329, slip op. (Fed. Cir. June 28, 2007), has **applied the TSM test after *KSR***. The Appellant in this declaratory judgment action argued that the claimed chemical compound was an obvious modification of a previously known compound—the modification requiring the substitution of a homolog in a different ring position. (*Id.* at 5.) The Federal Circuit rejected this, holding that "in cases involving new chemical compounds, it remains necessary to identify some reasons that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound." (*Id.* at 10.) Notably, the Court also rejected the Appellant's "obvious to try" argument, as the Appellant failed to demonstrate that one of ordinary skill would have chosen the prior art compound to modify from the millions of possibilities. (*Id.* at 15.)

Regarding motivation to modify properly combined references, **MPEP 2143** states that where the prior art conflicts, all teachings must be considered and that the fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness. **MPEP 2143** further states that there must be some suggestion or motivation to modify the references, and there must be a reasonable expectation of success. In addition, the prior art reference or references when properly combined, must teach or suggest all the claim limitations.

MPEP 2143.01 states that a proposed modification cannot render the prior art unsatisfactory for its intended purpose. If it does, then there is no suggestion or motivation to make the proposed modification. Further, the proposed modification cannot change the principle operation of a reference.

It is submitted that a proper case of *prima facie* obviousness has not been established because there is no motivation to modify the composition of Baru et al., which comprises a protein of polypeptide that is not encapsulated in colloidal particles, with the composition of Collins et al., which the include proteins embedded in the liposome membrane of the composition. *See* Collins et al. at Example I, column 15, lines 14-64.

Baru et al. is directed to a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and substantially neutral colloidal particles. According to Baru et al., a preferred protein is factor VIII, whose half-life is extended and which is protected from serum inhibitor antibodies by injecting it as a component of the composition. However, the compositions of Baru et al. require a protein or polypeptide that is ***not encapsulated*** in colloidal particles. *See* Baru et al., abstract.

However Collins et al. relates only to proteins capable of transitioning into the molten globular state. *See* Collins et al. at column 7, lines 41-54. Further, Collins et al. is directed to only negatively-charged liposomes. *See* Collins et al. at column 4, lines 30-45. In contrast, Baru et al. is directed to liposomes with substaintially no net charge. *See* Baru et al., abstract. Additionally, in Collins et

al., the hydrophilic polymer (=PEG) is bound to the protein to produce PEGylated G-CSF. *See* Collins et al. at column 8, lines 26-32. Finally, ***the proteins used in the composition of Collins et al. are embedded in the liposome membrane***. *See* Collins et al. at Example I, column 15, lines 14-64.

Applicants respectfully submit that there would be no motivation to modify the composition of Baru et al. with the composition of Collins et al. to achieve the present subject matter because doing so would change the change the principle operation of Baru et al. for at least the reason that Baru et al. requires a protein or polypeptide that is ***not encapsulated*** in colloidal particles; whereas Collins et al. requires proteins embedded in the liposome membrane. Changing the structure of the liposome of Baru et al. would likely change its properties and characteristics. Additionally, as Baru et al. requires substantially no net charge and Collins requires a negatively charged liposome, a skilled artisan would expect different characteristics of each composition. Charging the composition of Baru et al., as described in Collins et al. would likely change its mechanism of action. In this regard the Examiner is reminded of MPEP § 2143 which states that where the prior art conflicts, all teachings must be considered and that the fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness.

In view of the remarks set forth herein, it is submitted that, whether taken alone or in combination, Martin Baru et al. and Collins et al. do not render claims 28-33 and 39-43 obvious within the meaning of 35 USC § 103 (a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

VII. Miscellaneous

Applicants note that in the Official Action, the Examiner does not formally reject claims 44, 45, 48, 49, or 52. In this regard, Applicants respectfully request that the Examiner provide clarification on the status of these claims.

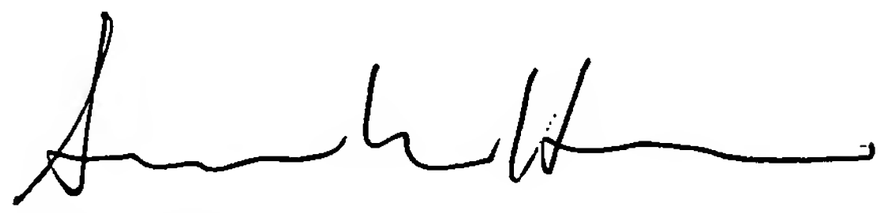
Conclusion

In view of the foregoing, Applicant submits that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicant petitions for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP



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